REMARKS

Applicant respectfully requests reconsideration.

Claims 13, 164, 485-512 and 515-520 were previously pending in this application. Claims 497-500 are cancelled. Claims 13, 164, 501, 502, 511, 512 and 515-520 are amended. Support for these amendments can be found at least on page 3 line 17 through to page 4 line 6, page 11 line 17, page 12 line 27, page 78 line 30 through to page 79 line 2, page 93 lines 2-15, and claims 499 and 500 as previously pending. No new matter has been added.

Claim Objection

Claim 13 is objected to for the recitation of "effective amount". Applicant has amended claim 13 to recite "an amount effective", as suggested by the Examiner. Applicant requests reconsideration and withdrawal of the claim objection.

Rejection under 35 U.S.C. §101

Claims 164, 502, 504, 506, 510, 512, 514, 516, 518 and 520 are rejected under 35 U.S.C §101 because, according to the Examiner, the claimed invention is not supported by a well established utility.

The Examiner interprets "preventing" an infectious disease to mean "that not a single virus, bacteria, fungus, parasite or prion can divide or propagate or replicate while present in the subject". This position is inconsistent with the definition of "prevention" provided in the specification on page 79. Notwithstanding this and without conceding to the Examiner's position but rather in the interest of expediting prosecution, Applicant has amended claim 164 to recite "reducing the probability that a subject will develop an infectious disease", as suggested by the Examiner.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112

Enablement

Claims 164, 502, 504, 506, 510, 512, 514, 516, 518, 520 are rejected under 35 U.S.C. §112 first paragraph because, according to the Examiner, "since the claimed invention is not supported by

a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention". Again, without conceding to the Examiner's position but rather in the interest of expediting prosecution, Applicant has amended claim 164 as suggested by the Examiner. In view of this amendment, claim 164 (and its dependent claims) possess a well established utility, as acknowledged by the Examiner, and thus one of ordinary skill in the art would know how to use the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 13, 164, 497-506 and 509-520 are further rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states that induction of IL-8/KC alone, as shown in FIG. 1, is insufficient to treat and/or prevent any infectious disease. The Examiner doubts the ability to treat subjects having an infectious disease and cites Wherry and Rupp as support. Applicants respectfully traverse.

The specification teaches how to make and use the claimed compositions, including the chemical structures of the claimed compounds, modes of administration, and exemplary infectious diseases to be treated or prevented according to the invention.

The claimed compounds are able to induce a cascade of cytokines and chemokines including IL-1, IP-10 and IL-6. Example 1 demonstrates only KC/IL-8 induction for the simple reason that "maximal increases in (KC/IL-8) serum levels have been observed to occur at 2 hours after Ile-boroPro administration, thereby allowing DPP-IV and KC assays of the same serum sample". The cytokines and chemokines induced by the claimed compounds are able to activate T cells, NK cells, macrophages and other antigen presenting cells, and are therefore able to stimulate immune responses in a subject. The role of pro-inflammatory cytokines such as IL-1, IL-6 and IL-8 in the management of infections is demonstrated in the attached abstracts. The claimed compounds therefore stimulate the immune system and can thereby enhance antigen-specific and non-antigen-specific immune responses. Such responses are not restricted to any particular antigen or infectious agent. The Examples demonstrate the ability of the claimed compounds to stimulate immune

responses in vivo and the efficacy of such immune responses against tumor cells. Similar immune responses would be expected to occur in vivo in the context of an infection.

The Examiner cites Wherry and Rupp to support the position that vaccination after an infection is established is not effective. Wherry documents therapeutic vaccination studies in a murine model of chronic infection with LCMV using a recombinant vaccinia virus that encodes an LCMV epitope, in the absence of an adjuvant. The reference teaches that therapeutic vaccination has potential positive effects on viral control. It further reports that the efficacy of the vaccination protocol is limited by high viral load and low proliferative potential of responding T cells. However it provides strategies for overcoming these limitations including lowering viral load by for example use of antiviral drugs and improving T cell function by for example immunotherapy. Importantly the reference speculates that different vaccination approaches that optimize antigen presentation or inflammatory signals may increase therapeutic vaccination efficacy. To this end, Applicants point out that the claimed compounds of the instant invention stimulate the induction of pro-inflammatory compounds which in turn are able to stimulate immune cells including T cells. The teachings of Wherry therefore support the use of agents such as those instantly claimed.

Rupp is cited for the observation of an HSV-2 vaccine that is effective in seronegative women but not effective in men or seropositive women. Rupp speculates that differences in vaccine efficacy may be due to the different adjuvants used. Adjuvants that induced "more robust Th-1-type cell-mediated responses" were more effective in the vaccination studies reported. To this end, Applicants point out that the claimed compounds of the instant invention stimulate induction of the Th1 cytokine IL-6 and activation of NK cells, T cells and macrophages, all of which are involved in immune response induction. The teachings of Rupp therefore support the use of agents such as those instantly claimed.

For at least these reasons, the claims are considered enabled based on the teachings in the specification and the state of the art at the time of filing. Reconsideration and withdrawal of the rejection is respectfully requested.

Indefiniteness

Claims 13, 164, 497-506 and 509-520 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and directly claim the subject matter which applicant regards as the invention.

Claims 13 and 164 are considered indefinite for the recitation of "agent". Without conceding to the Examiner's position and rather in the interest of expediting prosecution, Applicant has amended the claims to recite "compound" in place of "agent". As stated in the previous communication, Applicant intended an "agent" to be synonymous with a "compound".

Claims 13 and 164 are considered indefinite for the recitation of Am. Without conceding to the Examiner's position and rather in the interest of expediting prosecution, Applicant has amended the claims to recite A_m.

Claims 13 and 164 are considered indefinite for the recitation of "administering" and for the presumed failure to recite a carrier. Applicant points out that the prior amendment introduced the limitation of a pharmaceutically acceptable carrier into claims 13 and 164.

Claims 13 and 164 are considered indefinite for the recitation of "infectious disease". The specification defines and provides examples of infectious diseases to which the claimed invention relates. The term is therefore considered definite.

Claims 13 and 164 are considered indefinite for the recitation of "alphaketos". Claims 13 and 164 are now amended and the term alphaketo is no longer recited therein.

Claims 13 and 164 are considered indefinite for the recitation of "FAP". Claims 13 and 164 are now amended and the term FAP is no longer recited therein.

Claims 13 and 164 are considered indefinite for the recitation of "a concentration of above 10^{-8} M". The claims have been amended to recite "a serum concentration" of the compound. Support for this amendment can be found in Example 1 which demonstrates activity of Ile-boroPro in the serum of subjects administered the compound.

Claims 511 and 512 are considered indefinite for the recitation of "compounds" in view of the recitation of "compound" in claims 13 and 164. Claims 13 and 164 recite a composition comprising a compound of Formula III. One of ordinary skill in the medical art would recognize that such a composition comprises a plurality of such compounds and not just a single compound as

construed by the Examiner. Accordingly, the reference in claims 511 and 512 to more than one compound is reasonable and definite.

Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. §103

Priestley (USP 6,939,854)

Claims 13, 164, 503-506 and 509-520 are rejected under 35 U.S.C. §103 as being unpatentable over Priestley (USP 6,939,854). Claims 13 and 164 are amended to recite the formulae from claims 499 and 500, which were not rejected in view of Priestley. Reconsideration and withdrawal of the rejection is respectfully requested.

Wallner (USP 6,355,614)

Claims 13 and 164 are rejected under 35 U.S.C. §103 as being unpatentable over Wallner (USP 6,355,614).

Claims 13 and 164 are amended to recite that the infectious disease is not HIV infection. Support for this amendment can be found in the specification at least on page 12, line 27. Wallner teaches treatment of subjects in need of hematopoietic (including lymphoid) stimulation and proliferation. Wallner teaches treatment of subjects having HIV because this condition is "characterized by inadequate lymphocyte activation or concentration". (See col 12 lines 20-29.) Wallner does not teach treatment of subjects having an infectious disease other than HIV. Treatment of non-HIV infectious diseases would not be obvious at least because they are not commonly associated with below normal hematopoietic (including lymphoid) cell numbers.

Claim 164 relates to the prevention of infectious disease and therefore includes the limitation of a subject at risk of developing an infectious disease but not a subject already having such a condition. Wallner does not explicitly contemplate prevention of HIV, presumably because a subject not yet infected with HIV has normal hematopoietic cell numbers.

For at least the foregoing reasons, claims 13 and 164 are not rendered obvious by Wallner. Reconsideration and withdrawal of the rejection is respectfully requested.

Wallner (USP 6,355,614) in view of Simons, Preiser, Giles, Evans or Zaaijer

Claims 13 and 164 are rejected under 35 U.S.C. §103 as being unpatentable over Wallner (USP 6,355,614) taken together with any of the following: Simons P (*AIDS (London, England)*, Vol. 11, No. 14, pp. 1783-4, 1997); Preiser W. (*Journal of Medical Virology*, Vol. 60, No. 1, pp. 43-7, 2000); Giles R E (Journal of Medical Virology, Vol. 59, No. 1, pp. 104-9, 1999); Evans B.G. (BMJ (Clinical Research ed.), Vol. 315, No. 7111, pp 772-4, 1997); Zaaijer H. L. (Journal of Medical Virology 51(1), 80-82, 1997).

The rejection appears based on the recitation of the term "HIV-negative" as the Examiner considers that HIV-negative subjects may still be infected with HIV. Without conceding to the Examiner's position and rather in the interest of expediting prosecution, Applicant herewith amends claims 13 and 164 to recite that the infectious disease is not HIV infection. Support for this amendment can be found in the specification at least on page 12, line 27. The claims are not rendered obvious by Wallner taken together with the secondary references at least because the combination of references does not yield every limitation of the pending claims. Specifically, the combination does not yield the limitation of an infectious disease that is not HIV infection.

Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: April 13, 2007

Respectfully submitted,

By _____

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Appendix A

Biotherapy. 1994;7(3-4):161-7.

Interleukin-1 and related pro-inflammatory cytokines in the treatment of bacterial infections in neutropenic and non-neutropenic animals.

van der Meer JW, Vogels MT, Kullberg BJ.

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Bacterial infections in the immunocompromized host cause considerable mortality, and even the recently developed antimicrobial strategies often fail to cure these infections, especially in granulocytopenic patients. Cytokines and hematopoietic growth factors have been shown to stimulate host defense mechanisms in vitro and in vivo. We discuss the possible role of the pro-inflammatory cytokines interleukin-1, tumor necrosis factor-alpha, interleukin-6 and interleukin-8 as modulators of host resistance to bacterial infections. Interleukin-1 has been shown effective in various animal models of potentially lethal bacterial infection, even during severe granulocytopenia. The protective mechanism of interleukin-1 may be mediated via downregulation of cytokine receptors and cytokine production, and via induction of acute phase proteins. Moreover, in subacute and chronic infections interleukin-1 interferes with microbial outgrowth, via mechanisms that have only been partially elucidated.

PMID: 7865347 [PubMed - indexed for MEDLINE]

Related Links

Proinflammatory cytokines and treatment of disease. [Ann N Y Acad Sci. 1998] PMID:9917883

Interleukin-1 as a possible agent for treatment of infection. [Eur J Clin Microbiol Infect Dis. 1993] PMID:8477769

Cytokines in the treatment of fungal infections. [Biotherapy. 1994] PMID:7865351

[Immunology in clinical practice. VIII. Role of cytokines in the pathogenesis of bacterial infections] [Ned Tijdschr Geneeskd. 1998] PMID:9556983

Roles of tumor necrosis factor alpha, granulocyte-macrophage colony-stimulating factor, platelet-activating factor, and arachidonic acid metabolites in interleukin-1-induced resistance to infection in neutropenic mice. [Infect Immun. 1994] PMID:8168971

1: Biotherapy. 1994;7(3-4):195-210.

Cytokines in the treatment of fungal infections.

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Department of Medicine, University Hospital Nijmegen, The Netherlands.

The incidence of invasive fungal infections in the immunocompromized host has increased during the past decade. Even the recently developed antifungal drugs are unable to cure these infections in patients with severely impaired host defense mechanisms. Cytokines have great potential to augment host resistance and as adjunctive therapy of invasive mycoses. We discuss the mechanisms of host defense against invasive candidiasis, aspergillosis, and cryptococcosis, and review the use of cytokines and growth factors in this setting. Interleukin-1 has been shown effective in an animal model of disseminated candidiasis, even during severe granulocytopenia. Interferon-gamma has been very effective as a modulator of resistance against a variety of fungal infections in vitro. The effect of interferon-gamma against disseminated candidiasis has been demonstrated in a mouse model. Activation of neutrophils is the main mechanism by which interferon-gamma enhances the elimination of Candida, and consequently the agent is not effective in severely granulocytopenic animals. Data on the role of colony-stimulating factors against fungal pathogens are accumulating, and trials with these agents for hematologic patients with invasive fungal infections are now being performed.

PMID: 7865351 [PubMed - indexed for MEDLINE]

Related Links

Cytokines in immunodeficient patients with invasive fungal infections: an emerging therapy. [Int J Infect Dis. 2002] PMID:12718828

Design of efficacy trials of cytokines in combination with antifungal drugs. [Clin Infect Dis. 2004] PMID:15546121

Trends in immunotherapy of fungal infections. [Eur J Clin Microbiol Infect Dis. 1997] PMID:9063674

Pulmonary defense mechanisms against opportunistic fungal pathogens. [Immunol Ser. 1989] PMID:2490078

Antifungal immunity and adjuvant cytokine immune enhancement in cancer patients with invasive fungal infections. [Clin Microbiol Infect. 2007] PMID:17184281

1: Ann N Y Acad Sci. 1998 Sep 29;856:243-51.

Proinflammatory cytokines and treatment of disease.

van der Meer JW, Vogels MT, Netea MG, Kullberg BJ.

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Bacterial infections in the immunocompromised host cause considerable mortality, and even recently developed antimicrobial strategies often fail to cure these infections, especially in granulocytopenic patients. Cytokines and hematopoietic growth factors have been shown to stimulate host defense mechanisms in vitro and in vivo. The possible role of the proinflammatory cytokines interleukin (IL)-1, tumor necrosis factor-alpha, IL-6, and IL-8 as modulators of host resistance to bacterial infections is discussed. Interleukin-1 has been effective in various animal models of potentially lethal bacterial infection, even during severe granulocytopenia. The protective mechanism of IL-1 may be mediated by downregulation of cytokine receptors and cytokine production and induction of acute phase proteins. Moreover, in subacute and chronic infections IL-1 interferes with microbial outgrowth via mechanisms that have only been partly elucidated.

PMID: 9917883 [PubMed - indexed for MEDLINE]

Related Links

Interleukin-1 and related pro-inflammatory cytokines in the treatment of bacterial infections in neutropenic and non-neutropenic animals. [Biotherapy. 1994] PMID:7865347

Proinflammatory cytokines in the treatment of bacterial and fungal infections. [BioDrugs. 2004] PMID:14733604

Cytokines in the treatment of fungal infections. [Biotherapy. 1994] PMID:7865351

Critical roles of myeloid differentiation factor 88-dependent proinflammatory cytokine release in early phase clearance of Listeria monocytogenes in mice. [J Immunol. 2002] PMID:12244183

Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. [Exerc Immunol Rev. 2002] PMID:12690937